REMARKS

On page 16 of the Amendment filed on December 12, 2003, it was indicated that copies of the references referred to in the Appendix attached thereto would be provided as a supplement. Thus, copies of the references are attached hereto and Applicants provide the following additional remarks to put the teachings of the references in their proper context.

Maiese et al (Reference No. 1) suggests that rilmenidine may be useful for the treatment of stroke in a study comparing the effects of rilmenidine, idazoxan and SKF 86466, an α_2 antagonist. In the study, rats were pre-treated with one of idazoxan, rilmenidine or SKF 86466 and subjected to a model of stroke. It was found that the rats that were pre-treated with rilmenidine and with idazoxan suffered less damage. At that time, there was no clear explanation for difference in the effect between idazoxan and rilmenidine since both were thought to act at the I_2 receptor and the authors considered that one possible explanation of these results was that the effect might be mediated by I_2 receptors in the brain.

Craven and Conway (Reference No. 2), using another model, found that while idazoxan showed some neuroprotective effect, which could be explained by the degree to which the drug lowered the body temperature of the rats,[1] BU224 (a specific I_2 antagonist) and methoxyidazoxan (an α_2 antagonist) did not show a neuroprotective effect.

With respect to Craven and Conway, Applicants note that the authors were not able to show neuroprotective effects in the stroke model with idazoxan, an I_2 imidazoline receptor blocking drug, at the dosages studied. This is because idazoxan is an imidazoline compound which does of the not act at the I_3 oxazoline receptor and therefore the results discussed in the

[1] The hypothermic effect of idazoxan was previously described by Gustafson, "Blood Flow Metabolism", *J.Cereb.*, 1989;9:171-4.

Craven and Conway reference indirectly emphasize the positive neuroprotective effects reported with the I_3 oxazoline compounds used in the present invention, particularly those described in Table 2, submitted with the Amendment filed on December 12, 2003.

Craven and Conway is also helpful in explaining the work of Maiese et al, who found, in other models of experimental stroke, that idazoxan had some neuroprotective benefits but rilmenidine, which acts at the I_3 oxazoline receptor as well as the I_2 receptor, has greater benefits in protecting against damage from stroke because, at that time, there was no clear explanation for the difference in effect between idazoxan and rilmenidine since both were thought to act at the I_2 receptor. When the present inventors discovered that rilmenidine, but not idazoxan, had a major action at the I_3 oxazoline receptor, the additional benefits of rilmenidine could be explained. Thus, when taken together with the work of Craven and Conway, the results suggest that any benefit from idazoxan probably was not mediated by I_2 receptors, whereas rilmenidine clearly appears to provide neuroprotective benefits through its action at the I_3 oxazoline receptor. This conclusion is supported by Table 2, submitted with the Amendment filed on December 12, 2003, which shows a direct neuroprotective benefit of compounds active at the I_3 oxazoline receptor.

Additionally, a recent reference, Bousquet, P. et al., "Does It Make Sense to Develop New Centrally Acting Cardiovascular Drugs?", *J. Clin. Exp. Pharm. Physiol.*, 28:976-978 (2001), is submitted herewith which discloses the importance of drugs that act on imidazoline receptors in lowering blood pressure.

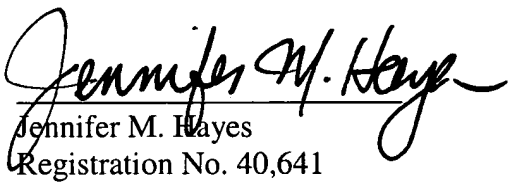
Thus, in view of the remarks previously made, the remarks herein and the attached references submitted herewith, Applicants respectfully submit that one of ordinary skill in the art would have been able to practice the claimed invention without undue experimentation.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, 1st paragraph.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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